https://doi.org/10.15360/1813-9779-2024-5-24-30

Effect of Succinate Crystalloid Solution on Hemostasis in Children with Severe Community-acquired Pneumonia

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For citation: *Vladimir V. Lazarev, Pavel E. Anchutin, Manuel M. Megeryan, Mikhail V. Bykov, Dmitry A. Smirnov, Tatiana A. Pchelicnceva, Nikolay S. Frolov, Khurzada M. Makhachilaeva, Boris I. Golubev, Elena A. Spiridonova.* Effect of succinate crystalloid solution on hemostasis in children with severe community-acquired pneumonia. *Obshchaya Reanimatologiya = General Reanimatology.* 2024; 20 (5): 24–30. https://doi.org/10.15360/1813-9779-2024-5-24-30 [In Russ. and Engl.]

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Summary

Aim of the study. To improve outcomes in children with severe community-acquired pneumonia (CAP) by including succinate-containing crystalloid solution (SCCS) in the treatment plan.

Materials and methods. The study included 100 patients diagnosed with CAP. SCCS was administered to 24 patients from the prospective (main) group, divided into 2 equal subgroups of 12 subjects who received SCCS with the infusion rate of 2.5 ml/kg/h (subgroup 1) and 5.0 ml/kg/h (subgroup 2). Treatment of 76 patients in the retrospective (control) group did not include SCCS.

Results. Greater decreases in D-dimer (by 418.5 ng/mL vs. 137.0 ng/mL, P=0.026) by day 3 and in fibrinogen (by 1.7 g/L vs. 0.2 g/L, P<0.001) by day 3 and (3.8 g/L vs. 0.5 g/L, P=0.002) by day 5 of hospitalization were found in children from the main group vs. the control group. Fibrinogen levels decreased in both study subgroups, although subgroup 1 had significantly higher fibrinogen levels on day 2 of ICU stay (P=0.034). A significant increase in activated partial thromboplastin time (aPTT) of 9.7 seconds was observed on day 3 in the main group versus 2.9 seconds in the control group (P<0.001). There was a direct correlation between fibrinogen level and neutrophil count on day 2 of ICU stay (R=0.479, P=0.033).

Conclusion. The use of SCCS in the treatment of severe CAP helps to prevent thrombotic complications, reduces hypoxia-induced changes in the coagulation system, and enhances the effects of unfractionated heparin. SCCS infusion at a rate of 5.0 mL/kg/h effectively reduces the levels of hypercoagulation markers, while its administration at a rate of 2.5 ml/kg/h potentiates the effects of unfractionated heparin. The effects of SCCS on hemostasis in severe CAP are equivalent to those of a moderate anticoagulant.

Keywords: succinate-containing crystalloid solution; inflammation; pediatric community-acquired pneumonia; hypercoagulation; meglumine sodium succinate; Reamberin

Conflict of interest. The authors declare no conflict of interest. NTFF POLYSAN LLC had no influence on the study design, analysis of the obtained data, interpretation of the results and writing the manuscript.

Introduction

Hypoxia is a common pathophysiological process that occurs in any critical illnesses, including infectious inflammation.

During inflammation and hypoxia, the energy metabolism of body cells undergoes a systemic rearrangement with suppression of aerobic glycolysis and oxidative phosphorylation [1]. This response is a defense mechanism found in all body cells, including immune cells and platelets, and is not designed for long-term function.

Inflammation and hypoxia lead to an increase in endogenous succinate (EnS) levels, which typically reach 20 μmol/L under normal conditions. EnS is a major pro-inflammatory signaling molecule that accumulates as a result of Krebs cycle arrest [2–4]. Regulation of the immune response is compromised under hypoxic stress conditions, resulting in coagulopathy, uncontrolled coagulation activation and thrombotic microangiopathy [5–7].

Cells of the immune system play an important role in the regulation of blood coagulation, in particular by promoting platelet thrombus formation [8-11]. Platelets are essential for the regulation of blood coagulation. Platelet aggregation is activated when endogenous succinate concentrations reach 300–500 μmol/L [12–15]. Monocytes [16, 17], neutrophils [18], lymphocytes and dendritic cells [19] are also important coagulation regulators.

Some clotting factors, such as thrombin, can directly activate immune cells, leading to increased production of proinflammatory cytokines [20]. Fibrin helps to recruit and activate immune cells at the site of injury or infection [21].

According to the World Health Organization, pneumonia is the leading cause of death in children

under the age of five worldwide. Severe pneumonia accounts for about 20% of deaths in children in the first five years of life. Deaths in children with pneumonia are more common during the active inflammatory phase [22].

Severe pneumonia is always associated with a high inflammatory response and an increased risk of arterial and venous thrombosis, including pulmonary embolism [23].

Normalizing the energy supply to the cell suppresses the production of inflammatory mediators, preventing an excessive immune response and, as a result, coagulation disorders. Exogenous succinate, as part of a succinate-containing crystalloid solution (SCCS), freely enters the cell and regulates energy metabolism, which benefits the coagulation system [23].

The aim of the study was to increase the efficacy of the treatment of children with severe community-acquired pneumonia (CAP) by adding a succinate-containing crystalloid solution (SCCS) to the treatment regimen.

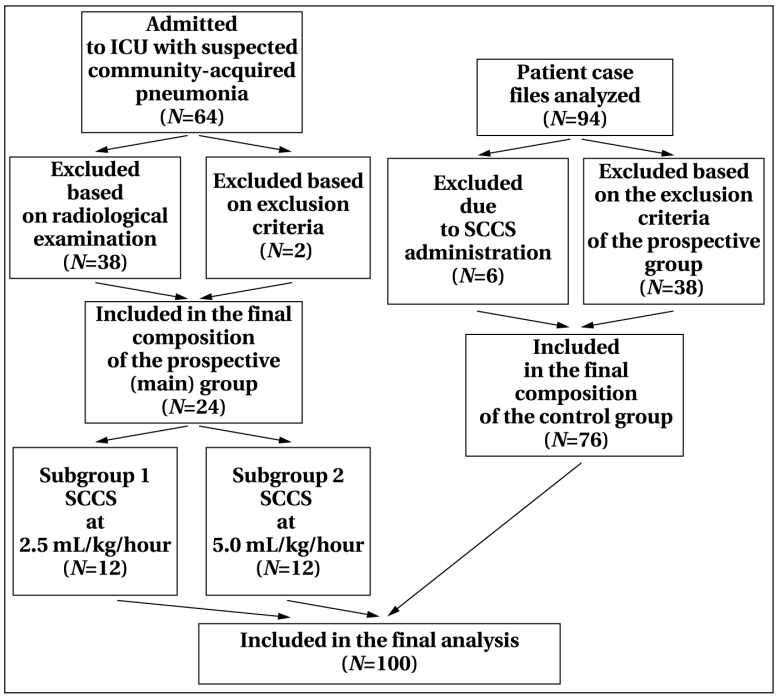

Fig. 1. Study flowchart.

Materials and Methods

We performed a retrospective-prospective, open-label, parallel-group, comparative study with patient stratification according to the mode of SCCS administration.

The study was conducted at the Podolsk Clinical Hospital from November 2021 to August 2023. The study included patients of both sexes aged 2 to 16 years with a confirmed diagnosis of severe community-acquired pneumonia who were admitted to the intensive care unit and required fluid therapy. Informed consent was obtained from the patient's legal representative.

Individual intolerance to the study drugs, traumatic brain injury with cerebral edema, renal dysfunction with changes in blood plasma electrolytes, urea, and creatinine, impaired blood acid-base balance such as alkalosis, pregnancy, lactation, and documented immunosuppression, both congenital and acquired, were non-inclusion criteria.

The prospective (main) group consisted of 24 patients with a confirmed diagnosis of CAP and indications for fluid therapy, which included an infusion of SCCS, meglumine sodium succinate (Reamberin 1.5%, OOO NTFF POLISAN), administered once daily at a total dose of 10 mL/kg per day, but not more than 400 mL.

Patients in the main group were divided into subgroups according to the rate of SCCS infusion using a random number table:

- Subgroup 1 (*N*=12): 2.5 mL/kg per hour
- Subgroup 2 (*N*=12): 5.0 mL/kg per hour.

The first SCCS infusion in each subgroup was given at the time of admission to the ICU, immediately after laboratory tests. Subsequent infusions were given once a day between 10:00 and 14:00. If necessary, the infusions of both subgroups were supplemented with 10% glucose and isotonic Sterofundin® solutions. The total daily fluid volume was limited to a maximum of 75% of the physiological requirement calculated according to the Holliday-Segar formula by continuous intravenous infusion throughout the day, with the exception of the SCCS administration.

The retrospective (control) group included 76 patients aged 2 to 16 years with a confirmed diagnosis of CAP and indications for fluid therapy who were previously treated in the intensive care unit between 2020 and 2023. Solutions containing 10% glucose and isotonic Sterofundin® were administered intravenously. The total amount of fluid infused each day was also limited to 75% of physiologic requirements.

To prevent venous thromboembolic complications, both groups received a continuous intravenous infusion of heparin sodium at a rate of 10 units/kg/hour from admission until transfer from the ICU, with the syringe changed every 6 hours.

Complete blood count and coagulation parameters such as activated partial thromboplastin time (APTT), international normalized ratio (INR), prothrombin index (PI), D-dimer, and fibrinogen were evaluated daily. Coagulation parameters were measured using a four-channel coagulation ana-

lyzer CoaTest-4 (Astra Research and Development Center, Russia).

Statistical analysis of the study results was performed using IBM SPSS Statistics v.26 and Microsoft Office Excel 2017 (Microsoft Corp., USA).

Due to non-normal distribution, quantitative parameters were presented as median and 25th and 75th quartiles *[Me (Q25; Q75)]*. Categorical variables were reported as absolute values and percentages (number, %).

Differences in qualitative parameters were evaluated using the Pearson χ^2 test or Fisher's exact test when the number of observations in a cell of the four-way table was <5.

Differences in quantitative parameters were calculated using the Mann–Whitney *U*-test. Multiple correlation analysis was performed using Spearman's rank correlation coefficient. To eliminate the influence of sex and age, additional pseudorandomization was performed by propensity score matching (PSM), resulting in the formation of groups comparable on these parameters. Differences were considered significant at $P<0.05$.

Results and Discussion

The groups were comparable in age (main group, 5.0 [2.8; 9.0] years; control group, 6.0 [4.0; 9.3] years, $P=0.298$); median body weight (main group, 19.5 [13.8; 28.3] kg; control group, 21.0 [16.0; 28.3] kg, $P=0.555$). The groups (main vs. control) were also comparable in the incidence of cerebral dysfunction (8.3% vs. 0.0%, $P=0.056$), circulatory disorders (4.2% vs. 0.0%, $P=0.240$), and metabolic disorders (4.2% vs. 0.0%, $P=0.240$). Male gender was predominant in the control group, 33.3% (8 patients) vs. 60.5% (46 patients) in the main group ($P=0.020$).

All patients in both groups had CAP (100.0%) and respiratory dysfunction (100.0%). The incidence of left-sided CAP in the main group was 20.8% (5 patients) and 21.1% (16 patients) in the control group ($P=1.0$); the incidence of right-sided CAP was 45.8% (11 patients) and 47.4% (36 patients), respectively ($P=0.895$); bilateral CAP was diagnosed in 33.3% (8 patients) and 31.6% (24 patients), respectively ($P=1.0$).

All patients in both groups received steroid, antibacterial, antiviral, and anticoagulant therapy with equivalent dosages and routes of administration.

Patients receiving SCCS had a more significant decrease in fibrinogen concentration on day 3 (by 1.7 g/L vs. 0.2 g/L, $P<0.001$) and day 5 of hospitalization (by 3.8 g/L vs. 0.5 g/L, $P=0.002$) compared to the control group (Fig. 2, *a*).

The main group also showed a more significant decrease in D-dimer concentration (by 418.5 ng/mL vs. 137.0 ng/mL, $P=0.026$) by day 3 of ICU stay compared to the control group (Fig. 2, *b*).

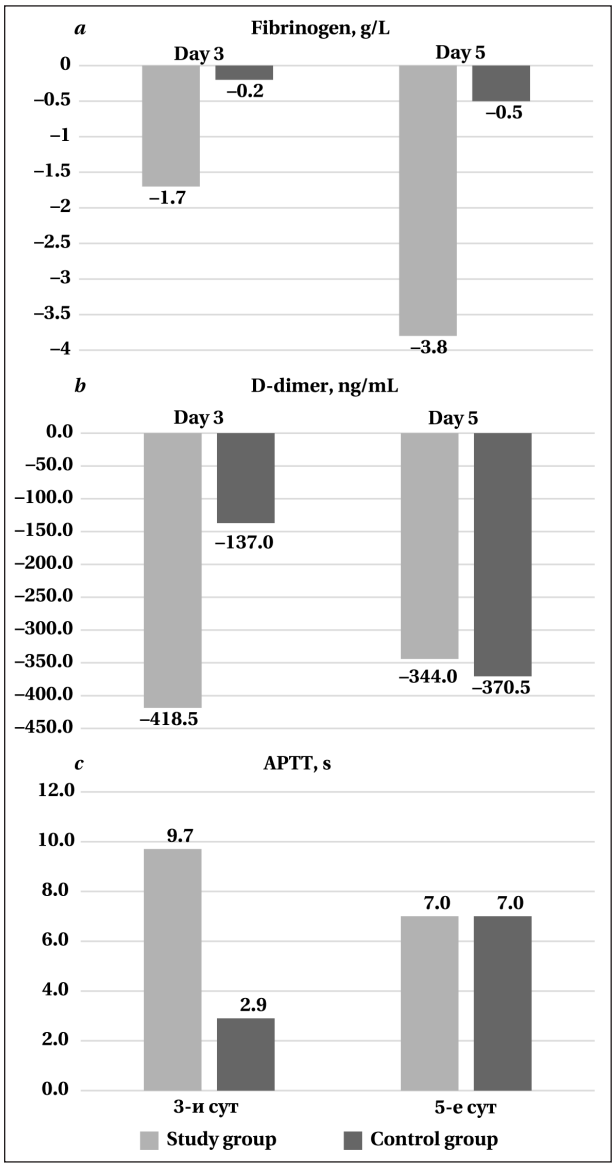

Fig. 2. Intergroup comparison of levels of fibrinogen *(a)*, D-dimer *(b)*, and APTT *(c)* on days 3 and 5 of hospital stay.

We found a significant increase in APTT on day 3 in the main group — by 9.7 seconds vs. 2.9 seconds ($P<0.001$) in the control group (Fig. 2, *c*).

PI values decreased by 25.6% in the main group and increased by 0.5% in the control group by day 5 ($P=0.018$).

Platelet count decreased by 63,000 cells in the main group and increased by 25,500 cells in the control group by day 3 ($P=0.045$), but by day 5 the decrease in platelet count was not statistically significant in either group.

Changes in coagulation parameters in the groups from the first to the fifth day of ICU stay are shown in Table 1.

Considering the significant sex differences between the groups, pseudorandomization was performed, resulting in the selection of 24 patients

Table 1. Changes in coagulation parameters in the study groups, *Me [Q1; Q3]*.

Day of ICU stay	Values in groups		*P*-value
	Main, *N*=24	Control, *N*=76	
Platelet count, 10^9/L			
1	316.0 [235.0; 361.3]	241.5 [204.0; 376.8]	0.236
2	308.5 [356.0; 344.0]	270.0 [202.8; 343.3]	0.053
3	312.0 [272.5; 418.0]	272.0 [190.5; 327.8]	0.026
4	354.0 [288.0; 398.0]	272.0 [187.5; 311.0]	0.014
5	296.5 [219.8; 335.8]	221.0 [183.0; 298.0]	0.373
Fibrinogen, g/L			
1	5.0 [4.5; 6.0]	4.1 [3.1; 5.3]	0.029
2	4.2 [3.6; 4.5]	4.1 [3.1; 5.1]	0.980
3	3.6 [2.7; 4.2]	4.2 [3.0; 4.9]	0.122
4	3.4 [2.9; 4.2]	4.0 [3.4; 4.4]	0.243
5	3.4 [2.9; 3.9]	4.0 [3.5; 4.7]	0.123
D-dimers, ng/mL			
1	624.0 [466.3; 819.8]	655.0 [441.0; 1140.5]	0.573
2	768.0 [590.5; 945.5]	1221.5 [1066.5; 1441.3]	0.267
3	225.0 [213.8; 254.5]	631.0 [476.0; 863.0]	0.001
4	115.0 [115.0; 115.0]	756.0 [482.5; 1131.5]	0.167
5	197.0 [192.5; 201.5]	991.0 [512.0; 1105.0]	0.095
APTT, s			
1	25.5 [22.1; 30.4]	28.4 [24.5; 34.2]	0.108
2	30.5 [28.5; 35.5]	30.4 [26.8; 34.1]	0.304
3	33.5 [32.0; 45.2]	32.3 [27.6; 35.3]	0.063
4	34.9 [29.0; 41.4]	33.9 [29.1; 36.4]	0.494
5	35.8 [31.5; 43.5]	33.9 [30.9; 37.6]	0.568
INR			
1	1.04 [0.95; 1.18]	1.1 [1.01; 1.18]	0.304
2	1.04 [0.95; 1.10]	1.11 [0.98; 1.16]	0.026
3	1.0 [0.9; 1.12]	1.05 [0.86; 1.14]	0.866
4	1.01 [1.0; 1.09]	1.04 [0.91; 1.12]	0.740
5	1.03 [0.96; 1.19]	1.01 [0.92; 1.1]	0.644
PI, %			
1	91.9 [86.5; 106.4]	97.0 [84.0; 108.0]	0.874
2	90.5 [84.8; 96.9]	94.5 [84.0; 104.0]	0.416
3	87.0 [83.0; 104.0]	93.0 [83.0; 104.0]	0.313
4	86.2 [85.0; 98.3]	97.5 [89.3; 105.0]	0.234
5	84.0 [78.9; 97.3]	97.5 [92.0; 105.3]	0.087

Note. For tables 1, 2, 3: APTT — activated partial thromboplastin time; INR — international normalized ratio; PI — prothrombin index.

from the control group who were comparable to the main group in terms of sex, age, and body weight. There were 33.3% (8 patients) males in the main group and 41.7% (10 patients) males in the comparison group (*P*=0.766). The median age was 5.0 [2.8; 9.0] and 6.0 [3.8; 10.4] years, respectively (*P*=0.220). The median body weight was 19.5 [13.8; 28.3] and 22 [14; 33] kg, respectively (*P*=0.687).

After pseudorandomization, there was an even more significant decrease in fibrinogen concentration (by 1.7 g/L vs. 0.8 g/L, *P*=0.040) and an increase in APTT (by 9.7 sec vs. 3.3 sec, *P*=0.007) in the main group compared with the control group on day 3 of hospitalization. We also observed a trend toward a reduction in PI in the main group by day 5 of hospitalization. However, the intensity of the decrease in D-dimer level (*P*=0.533), platelet count at day 3 (*P*=0.155), and fibrinogen at day 5 of ICU stay (*P*=0.144) did not differ between groups.

After adjustment for sex, the prospective group of children also maintained higher median platelet levels on days 2 (308.5 vs. 233.0×10^9/L, *P*=0.004), 3 (312.0 vs. 240.0×10^9/L, *P*=0.003), and 4 (354.0 vs. 231.0×10^9/L, *P*=0.010) of ICU stay. No decrease in platelet count below reference values was observed in either study group.

Subgroups of patients with different rates of SCCS infusion differed significantly in platelet counts on day 1 of observation: higher counts were observed in the subgroup with a lower rate of SCCS infusion (*P*=0.010, Table 2). On day 4, however, higher platelet counts were observed in the subgroup with a higher rate of SCCS infusion (*P*=0.010, Table 2).

A decrease in fibrinogen concentration was observed in both subgroups. However, on the 2nd day of ICU stay, lower values were recorded in the 2nd subgroup of the main group than in the 1st subgroup (*P*=0.034, Table 2).

The main group subgroups differed in APTT only on day 4: APTT was higher in subgroup 1 than in subgroup 2 (*P*=0.019, Table 2).

The subgroups of the main group differed in PI values only on day 1: it was higher in subgroup 2 than in subgroup 1 (*P*=0.027, Table 2).

There were no differences in INR values between the subgroups of the main group (Table 2).

Table 2. Changes in coagulation parameters in the subgroups of the study group, *Me [Q1; Q3]*.

Day of ICU stay	Subgroup of the study group		*P*-value
	1, *N*=12	2, *N*=12	
	Platelet count, 10^9/L		
1	345.0 [324.0; 371.8]	235.0 [199.0; 296.8]	0.010
2	315.0 [260.5; 411.3]	306.0 [255.3; 321.0]	0.443
3	315.0 [286.0; 463.5]	308.0 [275.3; 350.0]	0.397
4	290.0 [259.8; 313.5]	479.5 [398.0; 567.0]	0.010
5	273.0 [221.0; 296.5]	341.0 [271.5; 404.5]	0.4
	Fibrinogen, g/L		
1	5.5 [4.7; 6.1]	4.8 [3.8; 5.0]	0.283
2	4.4 [4.2; 4.6]	3.6 [3.2; 4.2]	0.034
3	4.0 [3.1; 4.2]	3.3 [2.4; 3.9]	0.397
4	3.1 [2.8; 3.5]	4.6 [4.3; 4.9]	0.143
5	2.9 [2.6; 3.4]	3.9 [3.4; 4.2]	0.4
	D-dimers, ng/mL		
1	624.0 [438.0; 887.5]	614.5 [563.5; 665.8]	1.0
	APTT, s		
1	27.3 [21.7; 31.1]	25.3 [22.5; 29.5]	0.976
2	31.1 [29.5; 38.5]	30.5 [28.5; 33.9]	0.456
3	40.1 [32.9; 45.3]	33.3 [29.6; 35.1]	0.299
4	40.0 [36.7; 43.0]	28.2 [27.1; 29.6]	0.019
5	40.0 [35.8; 42.3]	31.4 [29.6; 38.3]	0.7
	INR		
1	1.14 [0.95; 1.21]	1.03 [0.97; 1.11]	0.235
2	1.05 [0.95; 1.09]	1.04 [0.96; 1.11]	0.771
3	0.95 [0.89; 1.16]	1.0 [0.92; 1.12]	0.669
4	1.03 [1.0; 1.09]	1.01 [0.99; 1.1]	1.0
5	1.0 [0.91; 1.12]	1.05 [1.0; 1.21]	0.700
	PI, %		
1	87.5 [83.0; 104.3]	104.0 [91.5; 110.0]	0.027
2	88.5 [84.0; 93.9]	94.5 [87.0; 101.5]	0.346
3	90.0 [84.5; 104.0]	85.5 [83.5; 90.0]	0.417
4	85.2 [85.0; 93.3]	93.0 [79.0; 101.8]	0.610
5	79.0 [78.9; 92.5]	89.0 [73.5; 94.5]	1.0

Note. Rate of infusion of the SCCS: subgroup 1, 2.5 mL/kg/hour; subgroup 2, 5 mL/kg/hour.

Table 3. Correlation analysis of the relationship between neutrophil count and coagulation parameters.

Coagulation parameters	Neutrophil count		
	Day 1	Day 2	Day 3
Platelets	*R*=–0.185, *P*=0.409	*R*=–0.048, *P*=0.828	*R*=0.089, *P*=0.754
Fibrinogen	*R*=0.229, *P*=0.317	*R*=0.479, *P*=0.033	*R*=0.496, *P*=0.071
D-dimers	*R*=0.236, *P*=0.511	—	*R*=–0.400, *P*=0.600
APTT	*R*=–0.195, *P*=0.385	*R*=–0.206, *P*=0.370	*R*=–0.359, *P*=0.188

Correlation analysis was performed to assess the relationship between inflammation and coagulation parameters. The data are presented in Table 3.

There was a direct correlation between fibrinogen levels and neutrophil counts on day 2 of ICU stay, with a similar trend observed on day 3. The increase in fibrinogen levels not only reflects a tendency toward hypercoagulability, but also serves as an indicator of the intensity of the inflammatory response.

The complex interaction between the coagulation system and inflammation has important scientific and clinical implications. Infection-associated coagulopathy is closely related to the systemic inflammatory response syndrome, which is characterized by excessive release of cytokines and chemokines, increased production of interleukin-6 and -7, tumor necrosis factor-alpha, inflammatory chemokines, and hyperactivation of monocytes and macrophages [24, 25]. Accumulation of EnS leads to stabilization of hypoxia-inducible factor-1 alpha [26]. One way to correct an excessive inflammatory response and consequently hypercoagulation is to treat cellular hypoxia with exogenous succinate (ExS). As a component of SCCS, ExS normalizes the energy supply of immune cells and platelets, restores electron transfer chain function, suppresses glycolysis, and helps regulate hypoxia-inducible factor-1 alpha stability [27, 28].

Administration of SCCS was associated with potentiation of the effect of heparin. A similar therapeutic result was observed by other authors, who did not find potentiation of antiplatelet antibody production [29].

The use of SCCS as an adjuvant treatment for severe pneumonia in children helps to effectively eliminate systemic cellular energy deficiency.

Conclusion

Positive changes in coagulation parameters confirm the efficacy of SCCS (meglumine sodium succinate) in the intensive treatment of children with severe CAP. SCCS administration at a rate of 2.5 mL/kg/hour enhances the effect of prophylactic doses of unfractionated heparin (10 units/kg/hour). SCCS infusion at a rate of 5.0 mL/kg/hour results in a decrease in fibrinogen concentration.

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Received 22.01.2024
Accepted 16.08.2024